Efficacy of Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer by BRCA and Homologous Recombination Status: PRIMA/ENGOT-OV26/GOG-3012 Study

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PARPi: From Recurrent OC to 1L Setting

• Niraparib was the first PARPi approved as maintenance for recurrent OC regardless of biomarker status, on the basis of the NOVA trial
  • gBRCAmut: hazard ratio 0.27 (95% CI 0.17–0.41, P<0.001)
  • Non-gBRCAmut: hazard ratio 0.45 (95% CI 0.34–0.61, P<0.001)

• On the basis of QUADRA trial results, niraparib is approved for advanced OC treated with ≥3 prior lines of chemotherapy and for cancer that is HRd, defined by either a deleterious or suspected deleterious BRCA mutation or genomic instability and platinum sensitivity
  • Platinum-sensitive BRCAmut ORR, 39%; platinum-sensitive HRd ORR, 26%; duration of response, 9.4 months

• In the PRIMA trial, niraparib provided a clinically significant improvement in PFS in advanced OC after response to 1L platinum-based chemotherapy in the overall population (ITT)
  • HRd population: hazard ratio 0.43 (95% CI 0.31–0.59, P<0.001)
  • Overall population: hazard ratio 0.62 (95% CI 0.50–0.76, P<0.001)

**Hypothesis:** PRIMA/ENGOT-OV26/GOG-3012 tested the efficacy and safety of niraparib after response to platinum-based chemotherapy in newly diagnosed advanced OC, including patients at highest risk of relapse (ClinicalTrials.gov: NCT02655016)

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-grade serous or endometrioid adenocarcinoma on histology</td>
</tr>
<tr>
<td>• Stage III: PDS with visible residual disease after surgery or NACT or inoperable</td>
</tr>
<tr>
<td>• Stage IV: PDS regardless of residual disease, NACT, or inoperability</td>
</tr>
<tr>
<td>• CR or PR after platinum-based 1L treatment</td>
</tr>
<tr>
<td>• Tissue for homologous recombination testing was required at screening (Myriad myChoice®)</td>
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</table>

<table>
<thead>
<tr>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with stage III disease who have had complete cytoreduction (ie, no visible residual disease) after PDS</td>
</tr>
</tbody>
</table>

1L, first-line; CR, complete response; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PDS, primary debulking surgery; PR, partial response.
PRIMA Trial Design

**Patients with newly diagnosed OC at high risk for recurrence after response to 1L platinum-based chemotherapy**

**2:1 Randomization**

- **Niraparib**
- **Placebo**

**Endpoint assessment**

- **Primary endpoint:** PFS by BICR
- **Key secondary endpoint:** OS
- **Secondary endpoints:** PFS2, TFST, PROs, safety

**Stratification factors**

- NACT administered: yes or no
- Best response to 1L platinum therapy: CR or PR
- Tissue homologous recombination test status: HRd or HRp/HRnd
  - Determined by Myriad myChoice® next-generation sequencing test

**Protocol amendment, November 2017**

One-third of patients enrolled received the following starting dose:

- Body weight ≥77 kg and platelet count ≥150,000/μL: 300 mg QD
- Body weight <77 kg and/or platelet count <150,000/μL: 200 mg QD

**Hierarchical PFS testing**

- **Patients with HRd tumors**, followed by the ITT/overall population
  - Statistical assumption: a hazard ratio benefit in PFS of:
    - 0.5 in patients with HRd tumors
    - 0.65 in the overall population
  - >90% statistical power and one-sided type I error of 0.025


1L, first-line; BICR, blinded independent central review; CR, complete response; HRd, homologous recombination deficient; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.
PRIMA Enrollment and Outcomes

733 patients were randomized

5 did not receive intervention

728 received intervention

370 HRd

5 did not receive intervention

3 HRd

484 received niraparib

245 HRd

177 (37%) still receiving niraparib at data cutoff

121 HRd

244 received placebo

125 HRd

69 (28%) still receiving placebo at data cutoff

42 HRd

307 discontinued*

• 58 (12%) due to AE
• 218 (45%) due to PD
• 12 patient request

124 HRd

• 27 due to AE
• 80 due to PD
• 8 patient request

121 HRd

175 discontinued*

• 5 (2%) due to AE
• 162 (66%) due to PD
• 1 patient request

83 HRd

• 2 due to AE
• 76 due to PD
• 0 patient request

42 HRd

• Median follow-up of 13.8 months

Data cutoff: May 17, 2019.

*19 patients (8 HRd) and 7 patients (5 HRd) discontinued for other reasons in the niraparib and placebo arms, respectively.

AE, adverse event; HRd, homologous recombination deficient; PD, progression of disease.
### PRIMA Baseline Patient Characteristics and Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Niraparib (n=487)</th>
<th>Placebo (n=246)</th>
<th>Overall (N=733)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>62 (32–85)</td>
<td>62 (33–88)</td>
<td>62 (32–88)</td>
</tr>
<tr>
<td>Weight, median, kg</td>
<td>66</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Stage at initial diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>318 (65)</td>
<td>158 (64)</td>
<td>476 (65)</td>
</tr>
<tr>
<td>IV</td>
<td>169 (35)</td>
<td>88 (36)</td>
<td>257 (35)</td>
</tr>
<tr>
<td>Prior NACT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>322 (66)</td>
<td>167 (68)</td>
<td>489 (67)</td>
</tr>
<tr>
<td>No</td>
<td>165 (34)</td>
<td>79 (32)</td>
<td>244 (33)</td>
</tr>
<tr>
<td>Best response to 1L platinum-based CT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>337 (69)</td>
<td>172 (70)</td>
<td>509 (69)</td>
</tr>
<tr>
<td>PR</td>
<td>150 (31)</td>
<td>74 (30)</td>
<td>224 (31)</td>
</tr>
<tr>
<td>Residual disease after PDS or IDS,* n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No visible disease</td>
<td>224 (46)</td>
<td>117 (48)</td>
<td>341 (47)</td>
</tr>
<tr>
<td>Visible disease</td>
<td>220 (45)</td>
<td>112 (46)</td>
<td>332 (45)</td>
</tr>
<tr>
<td>No surgery</td>
<td>13 (3)</td>
<td>3 (1)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Homologous recombination test status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRd</td>
<td>247 (51)</td>
<td>126 (51)</td>
<td>373 (51)</td>
</tr>
<tr>
<td>BRCAmut</td>
<td>152 (31)</td>
<td>71 (29)</td>
<td>223 (30)</td>
</tr>
<tr>
<td>BRCAwt</td>
<td>95 (20)</td>
<td>55 (22)</td>
<td>150 (20)</td>
</tr>
<tr>
<td>HRp</td>
<td>169 (35)</td>
<td>80 (33)</td>
<td>249 (34)</td>
</tr>
<tr>
<td>HRnd</td>
<td>71 (15)</td>
<td>40 (16)</td>
<td>111 (15)</td>
</tr>
</tbody>
</table>

*44 patients had missing data (30 niraparib, 14 placebo).

1L, first-line; CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; IDS, interval debulking surgery; mut, mutant; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; PR, partial response; wt, wild-type.

**Overall:**
- 35% of patients had stage IV cancer
- 67% received NACT
- 31% achieved a PR to 1L platinum-based CT
- 51% had HRd tumors
- 30% had BRCAmut tumors
- 34% had HRp tumors
PRIMA Primary Endpoint: PFS Benefit in the HRd Population by BICR

57% reduction in hazard of relapse or death

<table>
<thead>
<tr>
<th></th>
<th>Niraparib (n=247)</th>
<th>Placebo (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>21.9 (95% CI 19.3–NE)</td>
<td>10.4 (8.1–12.1)</td>
</tr>
<tr>
<td>Patients without PD or death, %</td>
<td>6 months 86</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>12 months 72</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>18 months 59</td>
<td>35</td>
</tr>
</tbody>
</table>

Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

1L, first-line; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; HRd, homologous recombination deficient; NE, not estimable; PD, progression of disease; PFS, progression-free survival.
PRIMA Primary Endpoint: PFS Benefit in the ITT/Overall Population by BICR

38% reduction in hazard of relapse or death

<table>
<thead>
<tr>
<th></th>
<th>Niraparib (n=487)</th>
<th>Placebo (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>13.8 (11.5–14.9)</td>
<td>8.2 (7.3–8.5)</td>
</tr>
<tr>
<td>Patients without PD or death, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>12 months</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>18 months</td>
<td>42</td>
<td>28</td>
</tr>
</tbody>
</table>

Discordance in PFS event between investigator assessment and BICR ≈12%.

- High concordance between BICR and investigator-assessed PFS

Hazard ratio 0.62 (95% CI 0.50–0.76)
P<0.001

Niraparib
Placebo

PFS (%)
0 10 20 30 40 50 60 70 80 90 100

Initiation of PRIMA
after completion of 1L CT

Niraparib 487 454 385 312 295 253 167 111 94 58 29 21 13 4 0
Placebo 246 226 177 133 117 90 60 32 29 17 6 6 4 1 0

Initiation of PRIMA after completion of 1L CT

• High concordance between BICR and investigator-assessed PFS

Discordance in PFS event between investigator assessment and BICR ≈12%.

1L, first-line; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; ITT, intention-to-treat; PD, progression of disease; PFS, progression-free survival.
PRIMA Exploratory Analysis: PFS Benefit in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>Niraparib</th>
<th>Placebo</th>
<th>Hazard ratio for PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>487</td>
<td>246</td>
<td>0.62 (0.50–0.76)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>297</td>
<td>147</td>
<td>0.61 (0.47–0.81)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>190</td>
<td>99</td>
<td>0.53 (0.38–0.74)</td>
</tr>
<tr>
<td>Stage of disease at initial diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>318</td>
<td>158</td>
<td>0.54 (0.42–0.70)</td>
</tr>
<tr>
<td>IV</td>
<td>169</td>
<td>88</td>
<td>0.79 (0.55–1.12)</td>
</tr>
<tr>
<td>NACT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>322</td>
<td>167</td>
<td>0.59 (0.46–0.76)</td>
</tr>
<tr>
<td>No</td>
<td>165</td>
<td>79</td>
<td>0.66 (0.46–0.94)</td>
</tr>
<tr>
<td>Best response to platinum therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>337</td>
<td>172</td>
<td>0.60 (0.46–0.77)</td>
</tr>
<tr>
<td>PR</td>
<td>150</td>
<td>74</td>
<td>0.60 (0.43–0.85)</td>
</tr>
<tr>
<td>Homologous recombination test status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRd–BRCAmut</td>
<td>152</td>
<td>71</td>
<td>0.40 (0.27–0.62)</td>
</tr>
<tr>
<td>BRCA1mut</td>
<td>105</td>
<td>43</td>
<td>0.39 (0.23–0.66)</td>
</tr>
<tr>
<td>BRCA2mut</td>
<td>47</td>
<td>28</td>
<td>0.35 (0.15–0.84)</td>
</tr>
<tr>
<td>HRd–BRCAwt</td>
<td>95</td>
<td>55</td>
<td>0.50 (0.31–0.83)</td>
</tr>
<tr>
<td>HP</td>
<td>169</td>
<td>80</td>
<td>0.68 (0.49–0.94)</td>
</tr>
<tr>
<td>HRp</td>
<td>71</td>
<td>40</td>
<td>0.85 (0.51–1.43)</td>
</tr>
</tbody>
</table>

- Hazard ratios are clinically meaningful in all subgroups

CI, confidence interval; CR, complete response; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; mut, mutant; NACT, neoadjuvant chemotherapy; PFS, progression-free survival; PR, partial response; wt, wild-type.
PRIMA PFS in *BRCA1*mut and *BRCA2*mut

- Niraparib efficacy was similar in *BRCA1*mut and *BRCA2*mut

Hazard ratio 0.39 (95% CI 0.23–0.66)

Hazard ratio 0.35 (95% CI 0.15–0.84)

CI, confidence interval; mut, mutant; PFS, progression-free survival.
PRIMA PFS Benefit in HRd and HRp Subgroups by BICR

- Niraparib provided clinical benefit in the HRd (BRCA\text{mut} and BRCA\text{wt}) and HRp subgroups

- All subgroups were analyzed using the adjusted Cox regression method to account for stratification imbalances

**HRd BRCA\text{mut}**

- Hazard ratio 0.40 (95% CI 0.27–0.62)

**HRd BRCA\text{wt}**

- Hazard ratio 0.50 (95% CI 0.31–0.83)

**HRp**

- Hazard ratio 0.68 (95% CI 0.49–0.94)

---

**Legend:**
- Niraparib
- Niraparib, adjusted
- Placebo
- Placebo, adjusted

**Notes:**
- HRd BRCA\text{wt} population represents all HRd patients who are not BRCA\text{mut}.
- BICR, blinded independent central review; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; mut, mutant; PFS, progression-free survival; wt, wild-type.
PRIMA Safety: No New Safety Signals

- Dose interruptions were similar to those in the previous niraparib trials
  - Treatment discontinuation due to thrombocytopenia was 4.3%
- No treatment-related deaths
- One patient was diagnosed with MDS after 9 months of niraparib treatment

Thrombocytopenia and low platelet counts are not additive; some patients have both events.

TEAEs >20% incidence in niraparib arm. MedDRA-preferred terms.

MDS, myelodysplastic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
PRIMA Grade ≥3 TEAEs: Fixed vs Individualized Dosing

- Incidence of grade ≥3 hematologic TEAEs was lower in patients who received an individualized dose of niraparib compared with patients who received a fixed dose.

**Graph Description:**
- The graph illustrates the percentage of patients experiencing various hematologic TEAEs.
- Niraparib, fixed dose is represented by light blue bars.
- Niraparib, individualized dose is represented by green bars.
- Placebo, fixed dose is represented by pink bars.
- Placebo, individualized dose is represented by red bars.

**TEAEs Illustrated:**
- Thrombocytopenia
- Anemia
- Platelet count decreased
- Neutropenia
- Neutrophil count decreased
- Febrile neutropenia
- Myelodysplastic syndrome
- Pancytopenia
- Neutropenic sepsis

**Patient Counts:**
- Niraparib, fixed dose:
  - Thrombocytopenia: 36
  - Anemia: 36
  - Platelet count decreased: 16
  - Neutropenia: 15
  - Neutrophil count decreased: 9
  - Febrile neutropenia: 1
  - Myelodysplastic syndrome: <1
  - Pancytopenia: <1
  - Neutropenic sepsis: <1

- Niraparib, individualized dose:
  - Thrombocytopenia: 15
  - Anemia: 23
  - Platelet count decreased: 7
  - Neutropenia: 10
  - Neutrophil count decreased: 5
  - Febrile neutropenia: 0
  - Myelodysplastic syndrome: 0
  - Pancytopenia: 0
  - Neutropenic sepsis: 0

- Placebo, fixed dose:
  - Thrombocytopenia: 2
  - Anemia: 1
  - Platelet count decreased: 0
  - Neutropenia: 1
  - Neutrophil count decreased: 0
  - Febrile neutropenia: 0
  - Myelodysplastic syndrome: 0
  - Pancytopenia: 0
  - Neutropenic sepsis: 0

- Placebo, individualized dose:
  - Thrombocytopenia: 1
  - Anemia: 2
  - Platelet count decreased: 1
  - Neutropenia: 0
  - Neutrophil count decreased: 0
  - Febrile neutropenia: 0
  - Myelodysplastic syndrome: 0
  - Pancytopenia: 0
  - Neutropenic sepsis: 0

**Note:**
- TEAE, treatment-emergent adverse event.
Conclusions

- Niraparib demonstrated efficacy across biomarker subgroups in NOVA, QUADRA, and PRIMA clinical studies

- In PRIMA, niraparib demonstrated a clinically significant improvement in PFS after response to 1L platinum-based chemotherapy in **ALL** patients
  - PFS HRd: hazard ratio 0.43 (95% CI 0.31–0.59, P<0.001)
    - BRCA1mut: hazard ratio 0.39 (95% CI 0.23–0.66)
    - BRCA2mut: hazard ratio 0.35 (95% CI 0.15–0.84)
  - PFS overall population: hazard ratio 0.62 (95% CI 0.50–0.76, P<0.001)
  - PFS HRp: hazard ratio 0.68 (95% CI 0.49–0.94)

- Patients with OC at the highest risk of early disease progression (NACT, partial responders to 1L platinum-based chemotherapy) had significant clinical benefit with niraparib

- No new safety signals were observed; individualized dosing regimen reduced high-grade hematologic toxicities

- Niraparib monotherapy could be considered as a new opportunity after 1L platinum-based chemotherapy

1L, first-line; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; mut, mutant; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PFS, progression-free survival.
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